77. (Three Times Amended) A method of treating a tissue degenerative condition in a mammal comprising the step of administering a pharmaceutical composition to the mammal, whereby the composition treats the tissue degenerative condition in the mammal, the composition comprising:

a) a morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell in the mammal;

b) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein said MPSF is at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell; and

c) a pharmaceutically acceptable carrier.

REMARKS

Applicants have canceled claims 93, 94, 100 and 101. Applicants have canceled these claims without prejudice and without waiver of their right to file for and obtain claims directed to any canceled subject matter in divisional and continuing applications which claim priority from this application. As such, claims 69-88, 90, 91, 95-99 and 102-105 are pending in this application.

Applicants have amended claims 69, 74, 76 and 77 to clarify that the morphogenic protein stimulatory factor is present at a concentration effective to "synergistically" stimulate the tissue inductive abilities of the morphogenic protein. Support for this amendment is found in the alkaline phosphatase ("AP") assay results shown in Figures 1-10 and discussed at pp. 34-35 and 37 of the specification. Specifically, the application at p. 34, lines 12-18 recites:

> First, a MPSF is identified by picking one or more concentrations of a MPSF and testing them alone or in the presence of a morphogenic protein (**Examples 3 and 4**). Second, the amount of MPSF required to achieve optimal, preferably synergistic, tissue induction in concert with the morphogenic protein is determined by generating a dose response curve (**Example 3**). (boldface original; underscore added).

The results of the AP assays demonstrate that when present at certain concentrations, IGF-I, hydrocortisone, insulin and parathyroid hormone are capable of synergistically stimulating the tissue inductive activity of a morphogenic protein (see also discussions below). As emphasized during an interview with the Examiner on January 25, 2002, the novelty of the present invention lies in the unpredicted discovery that certain MPSFs induce a synergistic effect on the tissue-inductive activity of the morphogenic proteins.

Applicants have also amended claims 69, 74, 76 and 77 to specify that the MPSF is selected from the group consisting of "IGF-I, hydrocortisone, insulin and parathyroid hormone." Support for this amendment appears in claim 87 as originally filed and in the specification, e.g., in Figs. 1-5, 7-9, and in Examples 3-5 and 7-13 (pp. 71-77 and 85-95).

None of the amendments adds new matter. Applicants address the Examiner's rejections below:

35 U.S.C. § 112, 1st Paragraph: Claims 67-71, 74-80, 83-87, 90, 91 and 102-105

The Examiner has rejected claims 69-71, 74-80, 83-87, 90, 91 and 102-105 under 35 U.S.C. § 112, first paragraph for lack of enablement. Specifically, the Examiner states that the specification does not reasonably provide enablement for a method of inducing formation, repair or integration of any and all tissues other than bone, ligament and tendon.[3] More particularly, the Examiner states that Example 13 does not demonstrate nerve regeneration, and that nerve cells cannot be replaced if lost. Applicants traverse.

Applicants respectfully submit that claims 69-71, 74-80, 83-87, 90, 91 and 102-105 are enabled. First, numerous

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3 During the 1/25/02 interview, the Examiner again acknowledged that the specification is enabling for bone, ligament and tendon.

prior art studies have shown that neurons can be regenerated if damaged. In fact, Example 13 of the specification describes a method of determining the regeneration of damaged neurons. This method is similarly described in the cited prior art reference Wang (WO 95/05846).

During the January 25, 2002 interview, the undersigned presented and discussed some of the additional pre-filing references that demonstrate the ability of neurons to regenerate if damaged. These references were Lein, Derby and Lundborg.[4] Lein shows that OP-1 can not only promote dendritic regeneration of mature neurons, but also induce dendritic growth of naive neurons. Derby demonstrates that the rat sciatic nerve can be regenerated when damaged, and such a regeneration model can be used to monitor the effects of neural trophic factors such as NGF. Lunborg similarly observes anatomic and functional regeneration of a transected sciatic nerve following regrowth from its proximal stump. In sum, the prior art demonstrates that neural regeneration does occur in

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4 Lein et al., Neuron 15:597-605 (September 1995) (Exhibit C). This reference also describes that BMP/OP family members are important in neural development. For instance, OP-1, BMP-2, BMP-3, BMP-4 and BMP-5 are detected in at least one region of the brain, and BMP6 is expressed in most structures of the embryonic peripheral nervous system. Derby et al., Experimental Neurology 119:176-191 (1993) (Exhibit D). Lundborg et al., J. Hand Surgery 7:580-587 (1982) (Exhibit E).

adults. Furthermore, applicants discovered and now claim that the combined use of neural trophic morphogens with certain MPSFs promotes that regeneration.

Second, like bone, tendon and ligament regeneration, the promotion of neuron regeneration is only one of the many embodiments of the claimed invention. Applicants' invention can be used to enhance the tissue inductive activity of morphogenic proteins that act on other tissues. During the January 25, 2002 interview, the Examiner suggested that additional pre-filing references which demonstrate the diverse tissue specificity of BMPs would support applicants' position on the enablement issue.

Applicants hereby submit nine such references - Wang, Katagiri, Yamaguchi, Lyons, Ozkaynak, Jones, Maeno, King, and Schluesener.[5] These references collectively describe that:

- BMP-2 exhibits effect on adipocytes (Wang), muscle cells (Katagiri and Yamaguchi), chondrocytes (Wang

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5 Wang et al., Growth Factors 9:57-71 (1993) (Exhibit F). Katagiri et al., Journal of Cell Biology 127:1755-1766 (1994) (Exhibit G). Yamaguchi et al., Journal of Cell Biology 113(3):681-687 (1991) (Exhibit H). Lyons et al., Development 109:833-844 (1990) (Exhibit I). Ozkaynak et al., Journal of Cell Biology 267(35):25220-25227 (1992) (Exhibit J). Jones et al., Development 111(2):531-542 (1991) (Exhibit K). Maeno et al., PNAS 91:10260-10264 (1994) (Exhibit L). King et al., Developmental Biology 166:112-122 (1994) (Exhibit M). Schluesener et al., Atherosclerosis 113:153-156 (1995) (Exhibit N).

and Lyons), limb buds (Lyons), hair/whisker follicles (Lyons), heart cells (Lyons), and tooth buds (Lyons);

•BMP-3 plays a vital role in the liver and lung (Ozkaynak);

•BMP-4 exhibits effects on the liver and lung (Ozkaynak), hair/whisker follicles (Jones), heart (Jones), limb buds (Jones), pituitary gland (Jones), gut (Jones) and on erythropoiesis (Maeno);

•BMP-5 exerts effects on the liver, ureter, bladder and intestines (King); and

•BMP-6/Vgr-1 displays effects on the liver and lung (Ozkaynak), smooth muscle cells (Schluesener) and epithelial cells (Schluesener).

Thus, in light of the art at the time of the filing, the present specification clearly provides adequate enablement for using the claimed methods in tissues other than bone, ligament, tendon and neuron. All a skilled artisan needed to do was to use the recited MPSF with any of the numerous BMPs with known inductive activity in a tissue, to enhance that BMP's inductive activity in that tissue.[6]

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6 Applicants also note that an applicant need not demonstrate the operativeness of all species in the genus claim. MPEP § 2164.03.

Accordingly, applicants request that the Examiner reconsider the enablement rejection.

35 U.S.C. § 112, 2nd Paragraph, Claims 77-80, 83-87, 91 and 105

The Examiner has rejected claims 77-80, 83-87, 91 and 105 under 35 U.S.C. § 112, 2nd paragraph as being indefinite. Specifically, the Examiner contends that the claims "lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved." Applicants traverse.

Applicants respectfully submit that claims 77-80, 83-87, 90, 91 and 105 are definite. As discussed during the January 25, 2002 interview, the Examiner and his supervisor both agreed that the term "treats" does in fact recite the result to be achieved and that no amendments would be necessary. Accordingly, applicants request that the Examiner reconsider the indefiniteness rejection.

35 U.S.C. § 102(b): Claims 69-71, 77-80 and 83-87

The Examiner has rejected claims 69-71, 77-80 and 83-87 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,166,058 ("the Wang patent"). The Examiner has disregarded applicants' previous argument that the Wang patent

does not teach the use of IGF-I at a concentration effective to stimulate BMP-2 activity asserting that "all that the claims require is a morphogen and IGF-I, which is what Wang teaches." The Examiner also states that the features upon which applicants rely (i.e., stimulating BMP-2 or OP-1 activity, simulating AP activity) are not recited in the rejected claims. The Examiner further states that TGF-β and BMP synergize to promote the formation of endochondral bone *in vivo* based on Ogawa (Ogawa et al., Journal of Biological Chemistry 267(20):14233-14237). Applicants traverse.

Contrary to the Examiner's assertions, the rejected claims do recite specifically that the MPSF must be at a concentration "effective to stimulate" the tissue inductive activity of the morphogen. Notwithstanding, in the sole interest of expediting prosecution of this case towards allowance, applicants have amended claims 69, 74, 76 and 77 to recite that the MPSF must be present at an effective concentration to "synergistically" stimulate the tissue inductive activity of the morphogenic protein. Nowhere in the Wang patent is this feature even mentioned.

With respect to Ogawa, applicants respectfully submit that the Examiner's reliance on this reference is

improper. The amended claims of the present application do not recite TGF-β as a MPSF.

Thus, for all the above reasons, applicants request that the Examiner withdraw this novelty rejection.

35 U.S.C. § 102(e): Claims 77 and 85

The Examiner has rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 5,674,844 ("Kuberasampath 1"). The Examiner contends that "the features upon which the applicants [rely] (i.e., synergism) are not recited in the rejected claim(s)." The Examiner also contends that the term "beneficial" as used in Kuberasampath 1 and the term "MPSF" are indistinguishable. In addition, the Examiner contends that Ogawa suggests that TGF-β is an MPSF.

First, applicants have amended claim 77 to recite that the MPSF is present at a concentration effective to "synergistically" stimulate the tissue inductive activity of a morphogenic protein. This important feature is not taught in Kuberasampath 1.

Second, applicants respectfully submit that the terms "beneficial" and "MPSF" are distinguishable. Kuberasampath 1's "beneficial" is ambiguous and not clearly defined. Kuberasampath 1 merely discloses that factors known

to have a "beneficial effect on bone modeling" can be co-administered with a morphogenic protein. (see col. 4, lines 58-65). Many factors may be "beneficial on bone modeling," but not all of them can exert a synergistic effect on a morphogenic protein itself. For instance, these factors may have only algebraically additive, rather than synergistic, effects on a morphogenic protein. In short, Kuberasampath 1 does not contain an inkling of the notion that IGF-I, hydrocortisone, insulin and parathyroid hormone can synergistically stimulate the activity of a morphogenic protein.

Finally, with respect to Ogawa, applicants submit that the teachings of Ogawa are irrelevant. As discussed above, amended claims 77 and 85 do not recite TGF-β as a MPSF.

For all the above reasons, applicants request that the Examiner withdraw the 35 U.S.C. § 102(e) rejection.

35 U.S.C. § 103(a)

Claims 74 and 75: The Wang patent in view of Kuberasampath 2

The Examiner has rejected claims 74 and 75 under 35 U.S.C. § 103(a) as being obvious over the Wang patent in view of U.S. Patent 4,968,590 ("Kuberasampath 2"). The Examiner asserts that "[n]o difference is seen between 'agents

beneficial to the treatment of the bone defect,' i.e., IGF-I and a 'MPSF'." Applicants respectfully traverse.

As discussed above, amended claims 74 and 75 recite a method for accelerating allograft repair using a morphogenic protein and a MPSF selected from the group consisting of IGF-I, hydrocortisone, insulin and parathyroid hormone wherein the MPSF synergistically enhances the ability of the morphogenic protein. The Wang patent teaches compositions of BMP-2 and growth factors. The Wang patent does not teach synergism. Kuberasampath 2 discloses osteogenic devices containing pure osteogenic proteins. Kuberasampath 2 does not remedy the lack of teaching of synergism. Moreover, applicants respectfully submit that Kuberasampath 2 does not recite additional "agents beneficial to the treatment of the bone defect" as asserted by the Examiner. Accordingly, applicants request that the Examiner withdraw this rejection.

Claim 76: Rueger in view of the Wang patent

The Examiner has rejected claim 76 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent 5,344,654 ("Rueger") in view of the Wang patent. Again, the Examiner asserts that there is no difference "between 'agents beneficial to the treatment of the bone defects', i.e., IGF-I and a 'MPSF'." Applicants traverse.

Claim 76 recites a method of promoting *in vivo* integration of an implantable prosthetic device using a morphogenic protein and MPSF, wherein the MPSF synergistically stimulates the ability of the morphogenic protein to induce tissue formation. As already discussed above, the Wang patent does not teach synergism. Rueger teaches prosthetic devices coated with substantially pure osteogenic protein. Rueger does not teach MPSFs or that they synergistically stimulate the morphogenic protein's ability to induce tissue formation. Nothing in Wang or Rueger, either alone or in combination, teaches the method of claim 76. Accordingly, applicants request that the Examiner withdraw this obviousness rejection.

Claims 77, 90 and 91: Kuberasampath 1 in view of Hock, Baylink or the Wang Patent

The Examiner has rejected claims 77, 90 and 91 under 35 U.S.C. § 103(a) as being obvious over Kuberasampath 1 as applied to claim 77 and further in view of Hock et al., *Endocrinology* 122:254-60 (1988) ("Hock") and further in view of U.S. Patent 5,344,654 ("Baylink") or the Wang patent. According to the Examiner, "[n]o difference is seen between administering OP-1 together with other 'cofactors' known to have a beneficial effect on bone remodeling such as IGF-I and administering OP-1 with an 'MPSF'." Applicants traverse.

Kuberasampath 1 teaches that morphogens may be administered with cofactors that have a "beneficial" effect on bone remodeling. Hock teaches that IGF-I stimulates bone formation. Baylink teaches a bone implant material consisting of a growth factor selected from FGF, TGF-β, IGF-II or PDGF. The Wang patent teaches compositions of BMP-2 and EGF, FGF, TGF-α or TGF-β.

Amended claims 77, 90 and 91 recite a method of treating a tissue degenerative condition using a morphogenic protein and MPSFs selected from IGF-I, hydrocortisone, insulin and parathyroid hormone wherein the MPSF and morphogenic proteins act synergistically. This characteristic of the MPSF differs from cofactors which exhibit general beneficial effects on bone remodeling. None of the references identified by the Examiner, either alone or in combination, teaches a synergistic effect between morphogenic proteins and the four MPSFs recited in claims 77, 90 and 91.

Accordingly, applicants request that the Examiner withdraw this obviousness rejection.

35 U.S.C. §103(a)

Claims 69 and 102: The Wang patent in view of Kuberasampath 3

The Examiner has rejected claims 69 and 102 under 35 U.S.C. §103(a) as being obvious over the Wang patent as applied to claim 69 above and further in view of WO 91/18558 ("Kuberasampath 3"). The Examiner contends that the Wang patent teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I and is silent with respect to the carrier comprising heparin. The Examiner asserts that Kuberasampath 3 teaches a device comprising a carrier comprising heparin. On this basis, the Examiner states that it would have been obvious to combine the two references to arrive at the claimed invention. Applicants traverse.

Claims 69 and 102 recite a method for inducing local tissue formation wherein synergism exists between the morphogenic protein and specific MPSFs. As already discussed above, the Wang patent does not teach or suggest synergism, a key feature of the claimed invention. Kuberasampath 3 does not remedy this deficiency. Kuberasampath 3 teaches a method of growing bone using a device comprising heparin. Kuberasampath 3 does not disclose the specific MPSFs recited in claims 69 and 102. Nor does Kuberasampath 3 teach synergism between MPSFs and morphogenic proteins. Thus, the Examiner has not

established a *prima facie* case of obviousness against claims 69 and 102. Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 77 and 105: Kuberasampath 1 in view of Kuberasampath 3

The Examiner has rejected claims 77 and 105 under 35 U.S.C. §103(a) as being obvious over Kuberasampath 1 as applied to claim 77 and further in view of Kuberasampath 3. The Examiner contends that Kuberasampath 1 teaches a method of administering a composition comprising a carrier, morphogen and IGF-I and that Kuberasampath 3 teaches a device comprising a carrier comprising heparin. The Examiner asserts that one of ordinary skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants traverse.

Amended claims 77 and 105 recite a method of treating a tissue degenerative disease using a morphogenic protein and MPSF selected from IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein the MPSF synergizes the activity of the morphogenic protein. As discussed above, Kuberasampath 1 does not teach that the MPSF must be at a concentration effective to synergistically stimulate the tissue inductive activity of a morphogenic protein, as recited in amended claims. Kuberasampath 3, which is cited for teaching a device comprising a carrier comprising heparin, does not remedy

this deficiency. Accordingly, applicants request that this rejection be withdrawn.

Claims 74 and 103: The Wang patent in view of Kuberasampath

The Examiner has rejected claims 74 and 103 under 35 U.S.C. §103(a) as being obvious over the Wang patent and Kuberasampath 2 as applied to claim 74 above and further in view of Kuberasampath 3.

The Examiner contends that the Wang patent in view of Kuberasampath 2 teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I. In addition, the Examiner states that Kuberasampath 2 teaches a device comprising a carrier comprising heparin. The Examiner asserts that one of ordinary skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants traverse.

Claims 74 and 103 recite a method of accelerating allograft repair using a morphogenic protein and specific MPSFs wherein the morphogenic protein and MPSFs work synergistically.

As discussed above, the Wang patent does not teach the use of a composition containing a morphogenic protein and a MPSF that is at a concentration effective to synergistically stimulate the tissue inductive activity of the morphogenic protein, as recited in amended claims 74 and 103. Neither Kuberasampath 2 nor Kuberasampath 3 remedies this deficiency.

Kuberasampath 2 teaches osteogenic devices containing pure osteogenic protein. Kuberasampath 3 teaches a heparin matrix. Neither Kuberasampath 2 nor Kuberasampath 3 teaches MPSFs or their use to synergistically stimulate the tissue inductive activity of morphogenic proteins. Thus, the Examiner has not established a *prima facie* case of obviousness since the combination of these references does not teach synergism. Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 76 and 104: Rueger in view of the Wang patent and Kuberasampath 3

The Examiner has rejected claims 76 and 104 under 35 U.S.C. §103(a) as being obvious over Rueger in view of the Wang patent as applied to claim 76 above and further in view of Kuberasampath 3. The Examiner asserts that Rueger in view of the Wang patent teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I and that Kuberasampath 3 teaches a device comprising a carrier comprising heparin. The Examiner further asserts that one of ordinary skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants traverse.

Claims 76 and 104 recite a method of promoting in vivo integration using a morphogenic protein and MPSF selected from IGF-I, hydrocortisone, insulin and parathyroid hormone.

Rueger teaches prosthetic devices with substantially pure osteogenic protein. Rueger does not teach synergism, as recited in amended claims 76 and 104. As described above, neither the Wang patent nor Kuberasampath 3 teaches synergism to remedy this deficiency. Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 77 and 105: Kuberasampath 1 in view of Hock, Baylink, the Wang patent and Kuberasampath 3

The Examiner has rejected claims 77 and 105 under 35 U.S.C. §103(a) as being obvious over Kuberasampath 1 as applied to claim 77 and further in view of Hock and further in view of Baylink or the Wang patent and further in view of Kuberasampath 3. The Examiner contends that Kuberasampath 1 as applied to claim 77 and further in view of Hock and further in view of Baylink or Wang teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I. Kuberasampath 3 teaches a device comprising a carrier comprising heparin. The Examiner asserts that one of ordinary skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants traverse.

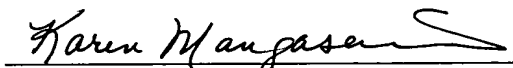
Claim 77 and 105 recite a method of treating a tissue degenerative disease using a morphogenic protein and MPSF selected from IGF-I, hydrocortisone, insulin or parathyroid hormone, wherein the MPSF synergizes the activity of the morphogenic protein.

As discussed above, Kuberasampath 1 does not teach that the MPSF must be at a concentration effective to synergistically stimulate the tissue inductive activity of a morphogenic protein, as recited in amended claims 77 and 105. Hock, Baylink, the Wang patent or Kuberasampath 3, either alone or in combination, do not remedy this deficiency. Accordingly, applicants request that the Examiner withdraw this rejection.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and grant allowance of the pending claims.

Respectfully submitted,



James F. Haley, Jr. (Reg. No. 27,794)
Karen Mangasarian (Reg. No. 43,772)
Attorneys for Applicants
c/o FISH & LEAVE
1251 Avenue of the Americas
New York, New York 10020
Tel.: (212) 596-9000

Appendix of Amended Claims

69. (Three Times Amended) A method for inducing local tissue formation from a progenitor cell in a mammal comprising the step of implanting in the mammal a morphogenic device at a locus accessible to at least one progenitor cell of the mammal, whereby the morphogenic device induces local tissue formation from the progenitor cell in the mammal, the morphogenic device comprising:

a) an implantable biocompatible carrier,

b) a morphogenic protein disposed in the carrier, the morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and

c) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of [hormones, cytokines, peptides and growth factors] IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein said MPSF is disposed in the carrier, and wherein [the] said MPSF [stimulatory factor being] is at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell[,

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone].

74. (Three Times Amended) A method of accelerating allograft repair and incorporation in a mammal, comprising the step of implanting at a locus in need of replacement bone a matrix-comprising device, whereby the device accelerates allograft repair and incorporation in the mammal, the device comprising:

a) an implantable biocompatible carrier,

b) a morphogenic protein disposed in the carrier, the morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and

c) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of [hormones, cytokines, peptides and growth factors] IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein said MPSF is disposed in the carrier, and wherein [the] said MPSF [stimulatory factor being] is at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell[,

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone].

76. (Three Times Amended) A method of promoting in vivo integration into a target tissue of a mammal an implantable prosthetic device, the method comprising the steps of:

a) providing on a surface of the prosthetic device an osteogenic composition, and

b) implanting the device in a mammal at a locus where the target tissue and the surface of the prosthetic device are maintained at least partially in contact for a time sufficient to permit enhanced tissue growth between the target tissue and the device,

wherein the osteogenic composition comprises (1) an morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and (2) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein said MPSF is at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell, and wherein said morphogenic

protein and MPSF are disposed on the surface region in an amount sufficient to promote from a progenitor cell enhanced tissue growth between the target tissue and the device[;

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone].

77. (Three Times Amended) A method of treating a tissue degenerative condition in a mammal comprising the step of administering a pharmaceutical composition to the mammal, whereby the composition treats the tissue degenerative condition in the mammal, the composition comprising:

a) a morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell in the mammal;

b) a morphogenic protein stimulatory factor selected from the group consisting of [hormones, cytokines, peptides and growth factors] IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein said MPSF [factor being] is at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell; and

c) a pharmaceutically acceptable carrier[;

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone].